

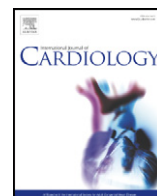
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## Editorial

## Vasospastic angina behaves differently in men and women



Angela H.E.M. Maas \*

Women's Cardiac Health Program, Department of Cardiology, Radboud University Medical Center, Nijmegen, The Netherlands

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The cardiology community has bypassed functional ischemic heart disease (IHD) over the past decades, being fascinated by all exciting interventional developments to manage obstructive coronary artery disease (CAD). Vasospastic angina, an important and frequently occurring functional manifestation of IHD, has been the playing field for passionate 'lone wolfs' in cardiology and for dedicated, mostly Asian or Japanese, research groups. Meanwhile coronary interventions have only solved part of the mechanisms of IHD and patients with recurrent, often unpredictable and variable symptoms of angina pectoris without obstructive CAD are still insufficiently recognized and treated. The diagnosis and treatment of vasospastic angina and other types of functional coronary disease is an ongoing frustration for both patients and their doctors.

In the current issue of the International Journal of Cardiology a Korean expert group of cardiologists in vasospastic angina report gender differences on its prognosis in 986 patients over a follow-up period of more than 11 years [1]. Clinical characteristics were importantly different among the 15% included women compared to the majority of males. Women were younger, had less obstructive CAD and needed a higher ergonovine dosage during provocative testing compared to men. Smoking was almost 8 times more prevalent in men, in whom hs-CRP levels were prognostic for adverse outcomes but not in women. Although the authors are to be praised for their large sample size and follow-up duration of patients with vasospastic angina, women represented only a minority and female-specific risk factors/variables were importantly lacking. Between the lines some interesting observations are noted in the Korean study: symptoms in women occurred more often at night with predominant spontaneous and inducible spasm in the RCA, which is also known from routine diagnostic coronary angiography. In men spasm was more often inducible in the RCX. In both genders it is striking to note that in only 1.6% of patients spontaneous

vasospastic attacks with ECG changes were present. This nurtures the uncertainty in optimally diagnosing vasospastic angina in clinical practice and underscores that inducible angina pectoris, ECG changes and/or spasm in the laboratory do not automatically reflect anginal symptoms in daily life. The prognostic association of hs-CRP in men may be more related to their higher rate of smoking, which enhances arterial inflammation, rather than sex-differences in hormonal status as stated by the authors. The majority of women in this study were postmenopausal, when sex-differences in hormonal status are less outspoken but still remain.

## 1. Role of sex steroids in modulating vasomotor response

Sex steroid hormones are increasingly acknowledged as being relevant to immune response and vascular inflammation, having a different impact in men and women during their lifetime [2,3]. Decreased levels of sex-steroid hormones are associated with a higher inflammatory state in both men and women. During the years of menopause transition there is a huge decline in estrogen levels, whereas the decline in testosterone levels with ageing in men is a more gradual process [4]. In adulthood men tend to have a higher inflammatory predisposition than women, but the opposite accounts for women after menopause [2]. Lower estrogen levels after menopause are related to altered vascular function, inflammation and upregulation of other hormonal systems such as the renin-angiotensin system (RAS) and the sympathetic nervous system [5]. In addition, female sex dominates in 80% of autoimmune disorders, which also enhances vascular endothelial dysfunction [2,6]. Evidence is increasing that coronary microvascular disease (CMD) is one of the key mechanisms involved in accelerated atherosclerosis in chronic inflammatory diseases [7]. The relatively higher proinflammatory state in women at middle-age results in a higher susceptibility to CMD than in men, whereas at older age when the traditional risk factors are more prevalent, obstructive CAD in the larger coronary arteries becomes the most common form of IHD. In contrast, vasospastic angina in the larger epicardial arteries occurs obviously more often in men than in women, also in Western populations, and may be provoked by their earlier appearance of non-obstructive atherosclerosis [8].

## 2. Role of psychosocial factors in functional ischemic heart disease

Although the male/female comparison is a crucial way to move forward in our understanding of the various manifestations of IHD, it is also interesting to understand why individual men or women are more prone to vascular dysfunction/vasospasm than others. Psychosocial,

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\* Corresponding author at: Women's Cardiac Health Program, Department of Cardiology, Radboud University Medical Center, PO Box 9101, Route 616, 6500 HB Nijmegen, The Netherlands.

E-mail address: [angela.maas@radboudumc.nl](mailto:angela.maas@radboudumc.nl)

socio-economic and behavioral factors may be even more relevant than pure biological sex-differences, which have always been the main focus of research. In the INTERHEART study psychosocial and stress-related factors were found to be important for IHD in both genders [9]. The prevalence of these factors is higher in women during their lifetime with a different impact on IHD than in men. Emotional activity has recently been shown to activate arterial inflammation, which is importantly involved in functional IHD [10]. Chronic psychological stress inhibits many functions of the immune system, which may enhance a higher susceptibility to endothelial dysfunction and vasospasm. Although stress-related factors were not studied by Lee et al., they may have been relevant to the observed clinical differences in angina presentation among men and women in their study group [1]. In clinical practice psychological and stress-related factors are more difficult to measure and quantify than the 'hard' figures of lifestyle and the traditional risk factors that we are used to work with. In our increasingly urban oriented way of life, personality traits, (job) stress and anxiety are inseparably connected to the world-wide increase in burden of IHD. This contains more than obstructive CAD alone and demands a different more patient-centered multidisciplinary approach than the secondary prevention measures nowadays indicate.

Optimal management of functional IHD, such as vasospastic angina and CMD demands a different and more open orientation of the cardiology community towards functional coronary testing, which has a low complication rate in hands of well trained and experienced intervention cardiologists [8].

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